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ADMINISTRATION OF 1-TYROSINE PREVENTS COLD-INDUCED MEMORY DEFICITS IN NAVAL SPECIAL WARFARE PERSONNEL

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TECHNICAL REVIEW AND APPROVAL

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The experiments reported herein were conducted according to the principles set forth in the current edition of the "Guide for the Care and Use of Laboratory Animals," Institute of Laboratory Animal Resources, National Research Council.

This technical report has been reviewed by the NMRI scientific and public affairs staff and is approved for publication. It is releasable to the National Technical Information Service where it will be available to the general public, including foreign nations.

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13. ABSTRACT *(Maximum 200 words)*

Thirty-six members of SEAL Team Two volunteered to serve as subjects in a field study to determine the efficacy of tyrosine to prevent cold-induced memory deficits. Members of three different platoons, over a three-year period of time, participated during annual Winter Warfare Training conducted in Alaska from January through March of each year. The subjects were first recruited, medically screened, and trained on a computerized cognitive performance assessment battery (PAB) at the Naval Amphibious Base, Little Creek, VA approximately one month prior to deploying to Alaska. Baseline test scores were obtained indoors under normothermic (70°F) conditions once training was completed. Once in Alaska the subjects were divided into two equivalent groups based on the test scores obtained during training. Both groups were then exposed to outdoor ambient cold temperatures, which ranged over the three years from approximately -22°C to -3°C (-10°F to 28°F), for one hour subsequent to consuming either 6.0 g of tyrosine or an equal amount of placebo. At the end of the cold exposure the subjects were brought inside and were administered the PAB. A 5 ml blood sample was obtained prior to consuming tyrosine or placebo and after

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13. completion of the test battery. The results indicate that consumption of tyrosine prevented cold-induced PAB deficits observed with the placebo group. On average the subjects who consumed placebo showed performance decrements on acquisition and memory tasks following cold exposure, while the subjects who consumed tyrosine had test scores comparable to those obtained under baseline conditions. Blood levels of tyrosine were elevated two- to three-fold in the tyrosine group compared with the placebo group 1.5 hrs after consumption; the blood levels of the two groups were comparable prior to consumption. The results indicate that consumption of a large bolus dose of tyrosine can prevent the inception of cold-induced cognitive performance deficits.

TABLE OF CONTENTS

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The research protocol employing human subjects in this study has been reviewed and approved by the Naval Medical Research Institute's Committee for the Protection of Human Subjects.

INTRODUCTION

Cold weather operations are of continuing concern to military planners, since they often constitute prolonged combined stressors. Cold exposure is often complicated by anxiety, fear, fatigue, sleep deprivation, and long distance travel. These multiple stressors predispose personnel to cognitive impairment and increase the probability of mistakes and accidents in the planning and execution of mission profiles. Naval Special Warfare personnel perform world wide cold climate missions. These missions can involve transitions from one climate to another, trans-meridian dislocation, altitude exposure, and continuous cold exposure. Transitions into cold environments have the potential to produce serious memory and performance deficits. The inability to recall or modify mission planning during cold exposure could jeopardize personal safety and mission success. Recent research on memory, with humans and animals, indicates that exposure to cold stress disrupts performance by impairing working memory (1, 2, 3, 4). In cold, forgetting is more profound the longer an individual is exposed. It is possible that cold-induced memory deficits could, at least in part, be ameliorated through nutritional or pharmacological intervention.

Endogenously produced neurotransmitters, such as norepinephrine (NE) and dopamine (DA), may act individually or in concert to affect memory processes (5). It has been hypothesized that exposure to stress may impair memory by depleting central nervous system (CNS) neurotransmitters in areas responsible for memory, such as the hippocampus and prefrontal cortex (6,7). Under conditions in which organisms are exposed to stressors, such as cold, NE turnover increases and NE levels become depleted (8, 9, 10, 11). In addition, research

has shown that DA and NE depletion in the prefrontal cortex of non-human primates impairs working memory (7, 12, 13).

The CNS levels of NE and DA depend on the level of the precursor amino acid tyrosine (14). Tyrosine crosses the blood brain barrier by means of a saturable transport mechanism that competes with other large neutral amino acids (15). Research has indicated that tyrosine administration may reverse stress-induced behavioral and cognitive effects by preventing the depletion of NE. For example, rats administered tyrosine prior to inescapable stressors, such as cold or shock exposure, do not show as much reduction in brain NE levels as rats not administered tyrosine (8, 14). Additionally, behavioral measures following acute stress indicate that rats given tyrosine are more active than rats exposed to the stressor without the benefit of tyrosine (9,10). Humans administered 100 mg/kg p.o. l-tyrosine and then exposed to a moderately cold stressor (e.g. 4700 m + 15° C) were less impaired on tasks requiring sustained attention, prior knowledge, spatial processing, verbalization, mathematical skills, and decision making (16). Research from our laboratory has demonstrated that tyrosine (50-200 mg/kg) could attenuate cold-induced memory deficits in rats (17). From these observations, one may hypothesize that tyrosine may reverse or at least minimize the effects of NE depletion by restoring its supply.

Tyrosine in dietary amounts is apparently safe and has no known toxic effect in humans (18). For example, a single-case, placebo-controlled, double-blinded crossover trial of 100 mg/kg/day of tyrosine for two weeks in a depressed patient produced no adverse effects (19). In another double-blinded pilot study, six depressed patients were given 100 mg/kg/day for four weeks with no major adverse effects. The only negative effect observed was mild epigastric

distress at the time of dosing, and this was alleviated by ingestion of the tablets with food (20). A single dose of tyrosine as high as 150 mg/kg has been given to humans without any noted side effects (21).

The purpose of this study was to evaluate the efficacy of an acute dose of 6.0 g of L-tyrosine as a prophylactic for the effects of cold stress on cognitive function.

METHOD

Subjects: Thirty-six males, ranging in age from 20 to 37 years, from the winter warfare platoons of FY 1992, 1993, and 1994, from SEAL Team Two, Naval Amphibious Base (NAB), Little Creek, VA, served as subjects. Data describing the subjects mean age, height, and weight when they were recruited into the study are described in Table 1.

TABLE 1

MEAN

	AGE	HEIGHT		WEIGHT	
YEAR	YEARS	CM	IN	KG	LB
1992	24.6	178.7	69.7	81.6	179.4
1993	25.5	179.3	69.9	83.1	182.7
1994	25.8	177.9	69.4	78.7	173.2
AVG	25.4	178.6	69.7	80.7	177.6

Procedure:

Preliminary Screening - Subjects' medical records were reviewed with attention to history of adverse reaction to drugs, other allergies, eye disease, skin abnormalities, nutritional problems, and cardiopulmonary conditions. Medical records were scrutinized to obtain reference baseline laboratory values for hematocrit, hemoglobin, leukocyte, platelet, and eosinophil counts,

and electrocardiographic data. Subjects with no contraindications then underwent a physical examination including measurement of height, weight, blood pressure, heart rate, and body temperature and when found physically qualified were accepted. No volunteers were rejected from participating in the study.

Baseline Data and Training:

Subjects were trained on a cognitive performance assessment battery (PAB) at their command (NAB, Little Creek, VA) prior to deploying for winter warfare training exercises. The preliminary training was essential for familiarization with the task and collection of baseline data. During this phase, each subject performed the PAB task for nine sessions over a three-day period.

For the first two years of the study the PAB consisted of two tasks, delayed-matching-to-sample (DMTS), and repeated acquisition (RA). The DMTS task always appeared first. During the final year the Environmental Symptoms Questionnaire, second revision (ESQIII) (22) was added to the PAB following the RA task.

DMTS: This task requires the subject to observe a sample stimulus consisting of an 8 X 8 matrix of filled and open squares for 1.5 seconds. Following a delay period of either 2, 8, or 16 seconds during which the computer screen is blank, the subject must choose the identical pattern as the sample stimulus from two comparison stimuli. The subject indicates his choice by pressing either the left or right arrow keys on the computer keyboard. The sample stimulus is always composed of half filled and half open squares. The pattern of squares is randomly generated by the computer before each trial. The non-matching comparison stimulus differs from the sample stimulus by two squares. One filled and one open square in the sample stimulus are reversed to

form the non-matching comparison stimulus. Each DMTS session consists of 60 trials equally divided between the three delay values. No time limit is placed on the subject while choosing between the comparison stimuli; however, the subjects are instructed to respond as accurately and as quickly as possible.

RA: The repeated acquisition task starts 20 seconds after the termination of the DMTS task. This procedure requires the subject to learn a different 12-member response sequence each session. The subject responds on the four arrow keys of the keyboard and receives visual feedback for each correct or incorrect response. The correct key sequence is chosen randomly by the computer from a list of 24 different sequences prior to each session. For instance, if the arrow keys are designated as up (U), down (D), left (L), and right (R), the correct sequence of responses on one session might be "ULDRDRULRDLU" and on the next session "LDURLRUDRULD." At the beginning of each trial a blank rectangle appears across the center of the computer screen. Each correct response fills in 1/12 of the rectangle and each succeeding correct response continues to fill in the rectangle from left to right. When the rectangle is completely filled in, the sequence has been completed correctly, the screen goes blank for 1.5 seconds, followed by the appearance of the blank rectangle outline signalling the beginning of the next trial.

The PAB was implemented on notebook computers. Each subject was provided with his own computer. Each training session was approximately thirty minutes in duration and was accomplished indoors at an ambient temperature of approximately 22°C.

ESQIII: This 67-item computerized symptom questionnaire, which takes approximately five minutes to complete, was added to the end of the PAB during the final year of testing. The

subject uses the number key pad of the computer to respond on a scale of 0 (not at all) to 6 (extreme) to questions like: "I feel dizzy," "My feet are cold," "I 'm shivering," or "Parts of my body feel numb." This scale was originally designed to diagnose acute mountain sickness. However, the data can be analyzed for other stress factors such as cold stress, as was done in this study.

TESTING

This phase of the project took place in the field, at a training site in Alaska. The training dates, dates of deployment, testing dates, and the ambient temperatures during the cold exposure prior to testing are presented in Table 2. The subjects completed a PAB retraining session on the day prior to tyrosine administration and were required to fast for six hours prior to tyrosine administration. On the morning of the test day the subjects had blood drawn and were administered either 6.0 g of L-tyrosine mixed in applesauce or 6.0 g of microcrystalline cellulose mixed in applesauce as placebo. They were then required to be outside for 60 minutes. During this time they were allowed to engage in any activity that was appropriate to their training. At the end of 60 minutes they were brought back inside, administered the PAB, and had a second 5 ml blood sample taken.

Aditionally, on one occasion, during year three, the subjects were divided into two groups of equivalent marksman, based on their most recent weapon qualification scores, and administered tyrosine or placebo prior to firing M-14s at 200 m pop-up silhouette targets.

TABLE 2

YEAR	DEPLOY	TEST 1 DATE	TEST 1 TEMP	TEST 2 DATE	TEST 2 TEMP
1992	13 JAN 92			03 MAR 92	-10°F(-23° C)
1993	07 JAN 93	09 JAN 93	28°F(-2°C)	14 FEB 93	22°F(-6°C)
1994	16 JAN 94	19 JAN 94	18°F(-8°C)	01 MAR 94	26°F(-3°C)

RESULTS

Ingestion of tyrosine prevented cold-induced performance deficits observed to occur with placebo. The effect of tyrosine or placebo on the accuracy of RA responding as measured by the number of error responses committed in a session is depicted in Figure 1. This figure presents the data collected during the final three baseline sessions at NAB, Little Creek (LC), VA, during the early phase of deployment to Alaska (AK1), and during the last phase of deployment to Alaska (AK3). The mean (SEM) number of error responses emitted during the baseline conditions were 33.6 (2.6), 28.1 (9.5), and 36.9 (4.2) during the LC, AK1, and AK3 conditions, respectively. Mean error levels in the placebo group were 45.8 (13.9) and 47.4 (10.4) during the AK1 and AK3 phases, respectively. Mean error levels in the tyrosine group were 29.0 (5.2) and 30.7 (5.9) during the AK1 and AK3 phases, respectively. The mean error levels in the tyrosine group were significantly lower than in the placebo group ($p=0.05$). The level of error responding in the tyrosine group was within the baseline range, actually toward the bottom of the baseline range, while the error levels observed with the placebo group were clearly elevated above both the baseline and tyrosine conditions.

The effect of tyrosine or placebo on session time with the RA task is presented in Figure 2. These data represent the mean time in seconds required to complete baseline or test sessions.

The average times (SEM) for the three baseline conditions were 360.6 (16.5), 313.2 (15.2), and 321.3 (20.0) seconds for the LC, AK1, and AK3 conditions, respectively. The data from the placebo group were 362.5 (37.9) and 305.6 (20.3) for the AK1 and AK3 conditions, respectively. The data from the tyrosine group were 347.3 (24.6) and 310.3 (26.6) for the AK1 and AK3 conditions, respectively. These data indicate that there was no significant difference ($p=>0.05$) in the amount of time required to complete sessions between the placebo and tyrosine groups.

The effect of tyrosine or placebo on DMTS accuracy of responding is depicted in Figure 3. This figure presents the combined average accuracy data, expressed as percent correct, for all subjects over the three years of the study. The top half of the figure presents the data for the placebo group and the bottom half the data for the tyrosine group. The data are grouped according to delay value, with the shortest value appearing to the left of the figure and the longest value on the right of the figure. Within each group of histograms the average baseline values obtained in Little Creek, VA appear on the left, the values from the first test in Alaska appear in the center, and the values obtained during the last test in Alaska appear on the right. The mean percent correct data (SEM) for the placebo group in the baseline condition were 81.8 (1.9), 80.2 (1.7), and 64.9 (2.5) for the two-, eight-, and sixteen-second delay conditions, respectively. The comparable data for the AK1 placebo condition were 78.2 (1.6), 70.9 (2.9), and 53.3 (2.8) and for the AK2 placebo condition were 78.6 (2.9), 69.2 (3.7), and 44.1 (2.9) for the two-, eight-, and sixteen-second delay conditions. Accuracy data for the tyrosine group in the baseline condition were 81.2 (1.9), 80.2 (1.7), and 64.8 (2.5) for the two-, eight-, and sixteen-second delay conditions, respectively. The comparable data for the AK1 tyrosine condition were 86.6 (2.0), 81.8 (2.9), and 66.0 (3.8) and for the AK2 tyrosine condition were 85.0 (1.6), 81.7 (2.2), and 69.2

(2.2) for the two-, eight-, and sixteen-second delay conditions, respectively. The mean accuracy of responding in the tyrosine group was significantly higher than in the placebo group ($p=.01$) with the 16-second delay condition. These data indicate that there was a cold-induced decrease in accuracy of responding in the placebo group that was prevented by the ingestion of tyrosine.

Accuracy data for the firing of one twenty round magazine per subject are presented in Figure 4. These data were collected only during the third year of the study. There were eight subjects in both the tyrosine and placebo groups. Each group therefore fired a total of 160 rounds. The groups were outside at the range for approximately 2 hours with an air temperature of 26°F before firing commenced. The tyrosine group achieved a score of 100% accuracy, hitting the targets with all 160 rounds. The placebo group missed 9 of the 160 rounds for an accuracy score of 94%.

The degree of cold stress subjectively experienced by the subjects is presented in Figure 5. These data were collected only during the third year of the study. Subjects indicated on a six point scale, with zero indicating no stress and six indicating extreme stress, how cold they felt. The left hand pair of histograms represent data collected early in the deployment and the right hand pair of histograms represents the data collected during the latter stages of deployment to Alaska. The open histogram in each pair represents data from the placebo group and the solid histograms represent data from the tyrosine group. The data indicate no difference in perceived cold between the groups during either phase of data collection. The perceived degree of coldness was significantly greater during the early phase of deployment than during the latter stage for both groups, indicating that cold acclimation occurred during the deployment.

Plasma levels of tyrosine are presented in the left half and the plasma ratio of tyrosine to five other neutral amino acids are presented in the right half of Figure 6. These data were collected during the early phase of deployment to Alaska. The open histograms represent the data from the placebo group, while the solid histograms represent data from the tyrosine group. The open and solid histograms on the left side of each figure half represent plasma tyrosine levels prior to the ingestion of tyrosine and the comparable histograms on the right side represent plasma levels approximately 90 minutes post ingestion. The data presented in this figure demonstrate that the plasma levels of tyrosine in the tyrosine group were approximately double those of the placebo group post ingestion. Similarly, the ratio of tyrosine to other amino acids was also approximately double post ingestion. There were no differences between the groups in either tyrosine plasma level or tyrosine ratio prior to tyrosine ingestion. The data presented in Figures 7 and 8 show similar results for data collected during the middle (Figure 7) and latter (Figure 8) stages of deployment.

CONCLUSIONS

The results indicate that exposure to cold in a field setting impaired the accuracy of performance of both acquisition and memory tasks when compared with baseline performance levels. These results are consistent with, and extend, the findings of previous studies showing that cold stress induces memory impairment in both animals and man in cold-chamber environments (1,2,3).

The administration of the catecholamine precursor amino acid tyrosine prior to cold exposure completely protected against the cold-induced accuracy deficits. Performance accuracy on the acquisition and memory tasks following tyrosine administration was comparable to levels

observed during baseline conditions. These findings are consistent with previous results obtained with animals and humans in laboratory cold environments (4,9,10,16,17). Neither cold stress nor tyrosine administration altered the amount of time subjects required to complete repeated acquisition sessions. These data demonstrate that a bolus dose of tyrosine administered prior to cold exposure in a field setting is capable of preventing cold stress-induced deficits in the acquisition and retention of information.

Previous research has demonstrated that acute stress exposure, including cold, reduces the concentration of NE and DA in certain regions of the CNS (10, 23, 24, 25) and that administration of tyrosine can restore levels of NE in the hippocampus, an area of the brain necessary for the formation of memory (10). Presumably, the depletion of catecholamine levels adversely affects the function of neurons in critical areas of the brain and therefore interferes with the normal process of memory creation and retention. However, the exact mechanisms underlying this process are not understood. A more detailed discussion of these issues may be found in (4).

The data describing the difference in target accuracy between the tyrosine group and the placebo group are preliminary but interesting. All eight subjects fired from a prone supported firing position; i.e., they were lying down on range platforms with their weapons supported by sandbags. There were no restrictions on the amount of time it took them to setup their position or the amount of time to expend the 20 rounds. Out of a total of 160 rounds fired by each group the placebo group only missed nine but the tyrosine group missed none. While the difference between the groups is not statistically significant, the practical difference on a battlefield could be the difference between mission failure or success.

While CNS levels of tyrosine could not be measured directly, the plasma levels of tyrosine and the ratio of tyrosine to five other large neutral amino acids determined before and after ingestion indicate that tyrosine was indeed present. The subjects who ingested tyrosine had approximately twice the plasma levels present in the placebo group and had a tyrosine ratio also approximately double that of the placebo group. The tyrosine ratio data are important because the transport mechanism for amino acids into the CNS is competitive and concentration dependent (26). The larger the concentration of each molecule, the more that gets transported across the blood brain barrier. The amino acid data suggest that large concentrations of tyrosine should have been present in the CNS. The data from the symptom questionnaire relating to perceived degree of cold stress were inconclusive. There were no differences between the tyrosine and placebo groups, but there was a difference between the early phase of deployment and the latter stage of deployment, possibly indicating cold acclimation. However, the degree of perceived coldness during the early phase was only approximately 1.0 on a 5.0 point scale, and approximately 0.2 during the late phase.

Given the success of tyrosine in preventing cold-induced cognitive deficits in this and other research (4, 8, 9, 16, 17, 23), supplemental administration of this amino acid to military personnel about to be exposed to acute cold stress would perhaps seem to be an appropriate prophylactic measure.

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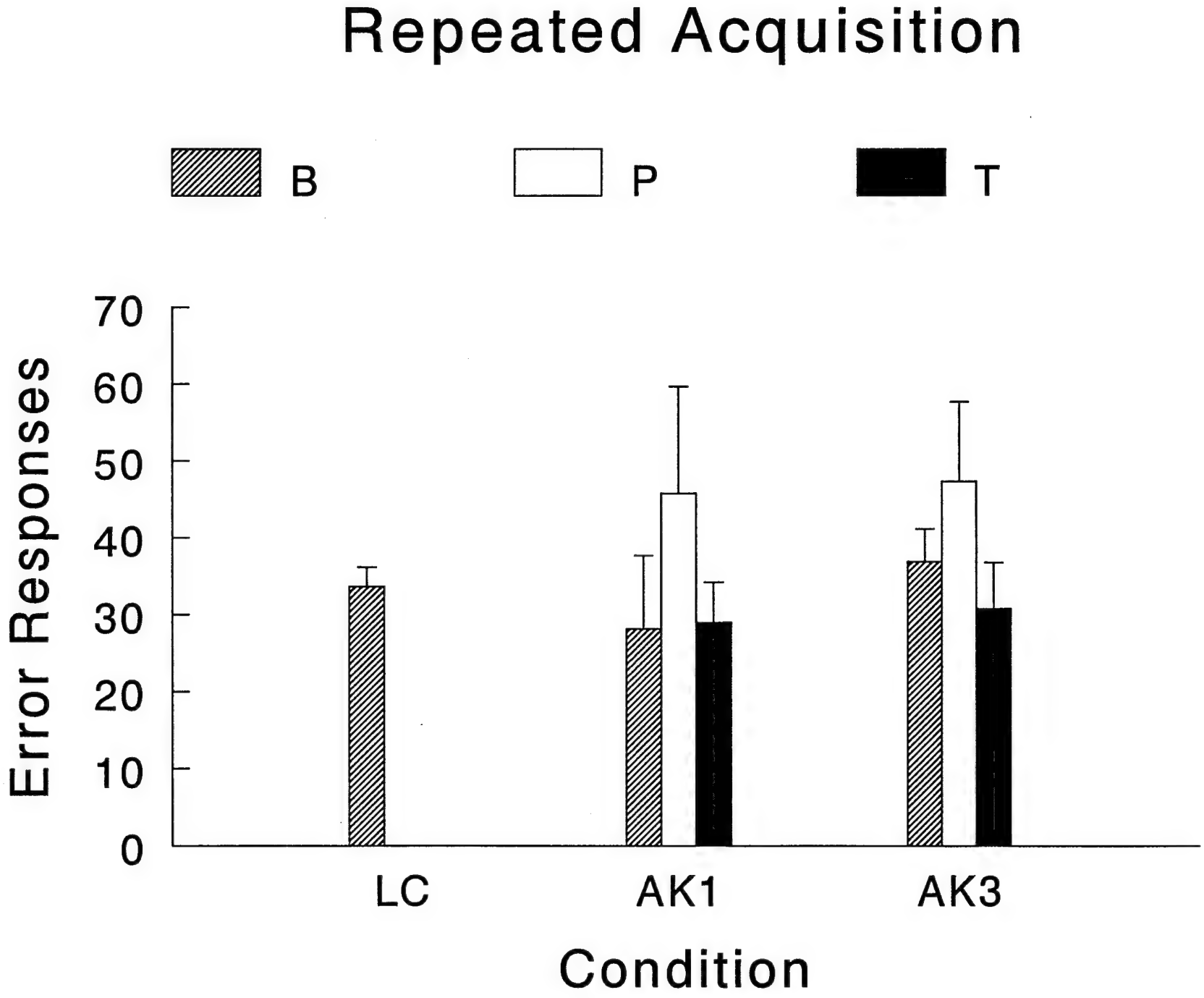
FIGURE 1


Repeated Acquisition
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Condition

FIGURE 2

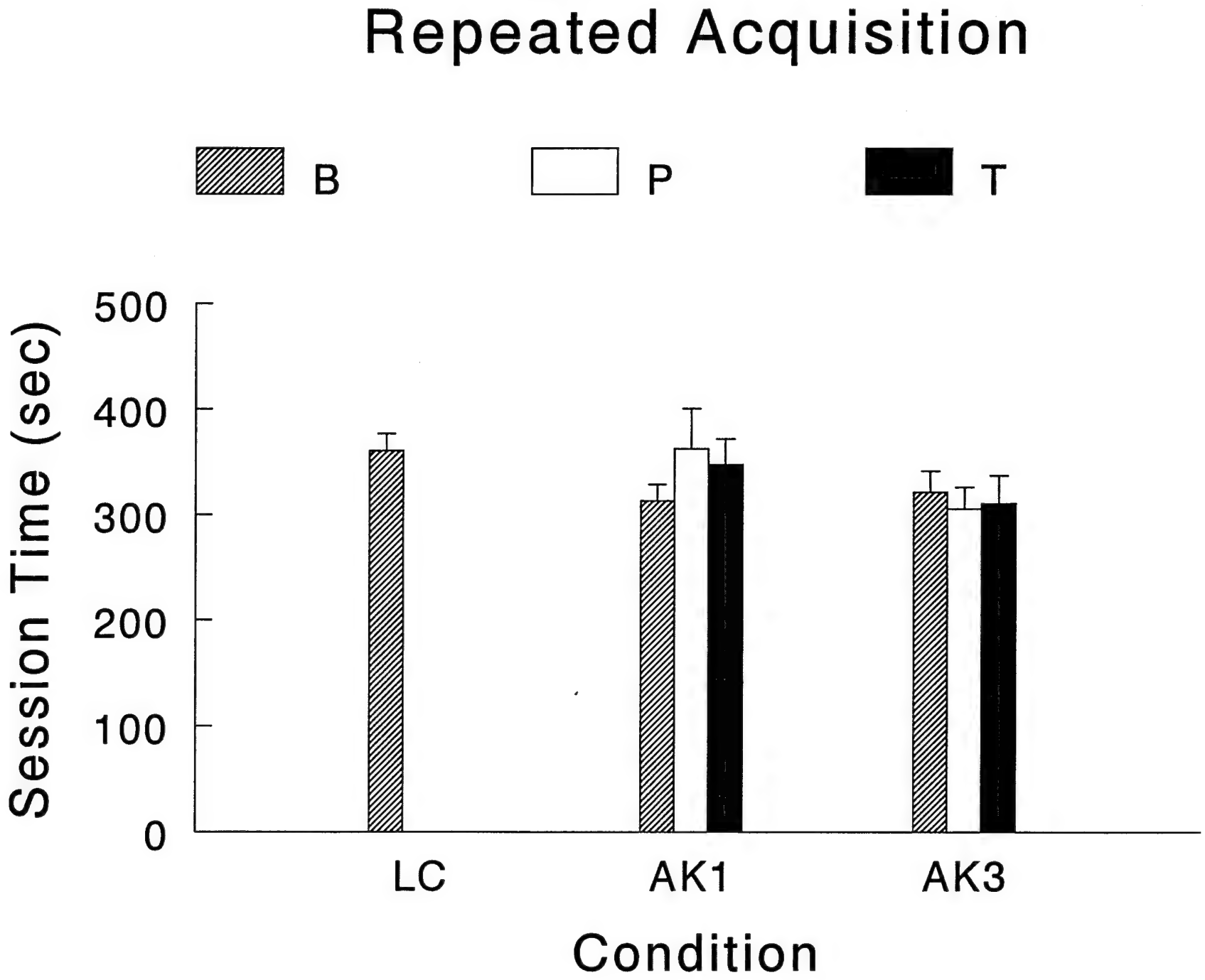
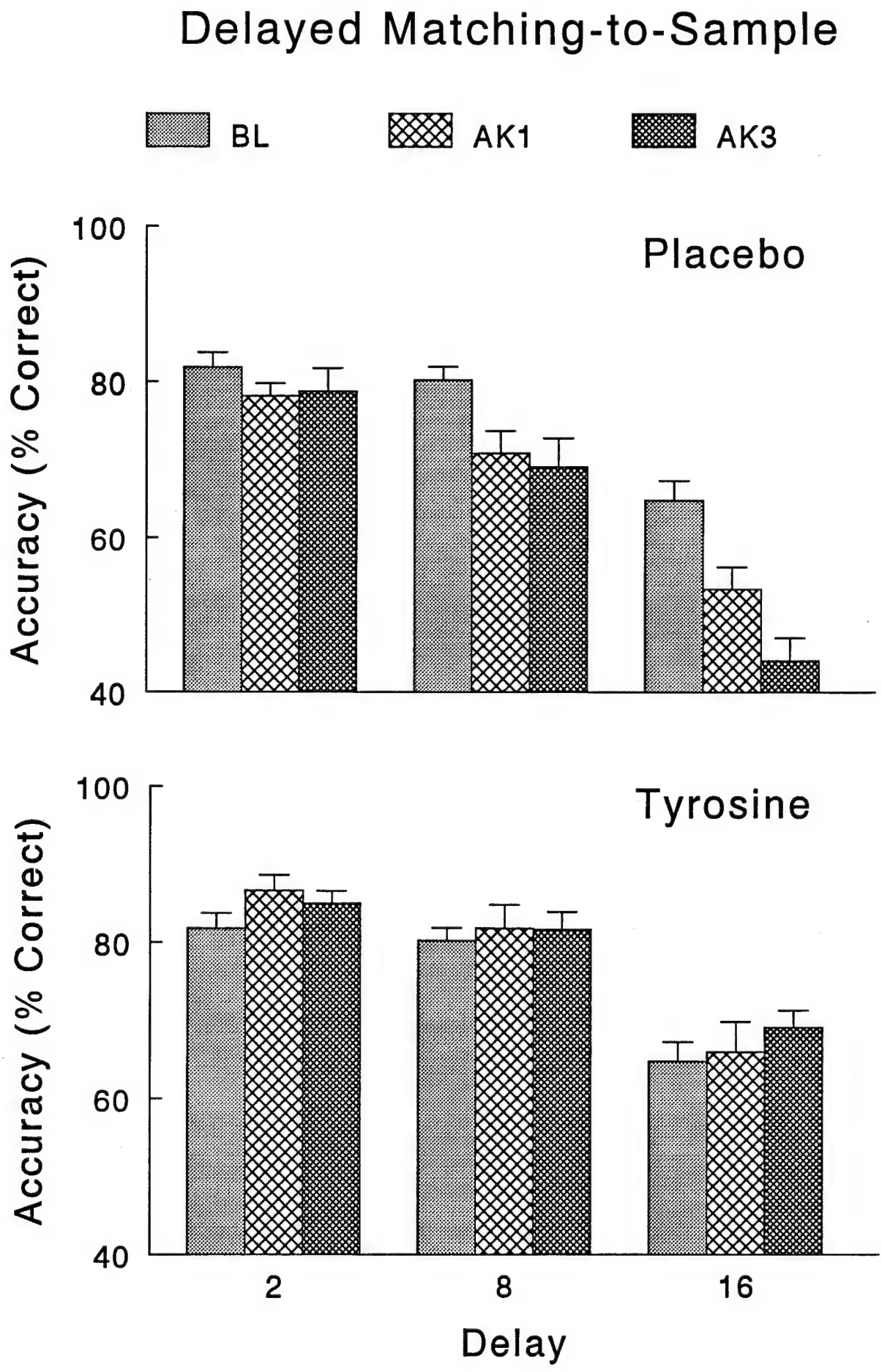

Repeated Acquisition
B
P
T
Session Time (sec)
500
400
300
200
100
0
LC
AK1
AK3
Condition

FIGURE 3


Delayed Matching-to-Sample
BL
AK1
AK3
Placebo
Tyrosine
Accuracy (% Correct)
100
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60
40
2
8
16
Delay

FIGURE 4

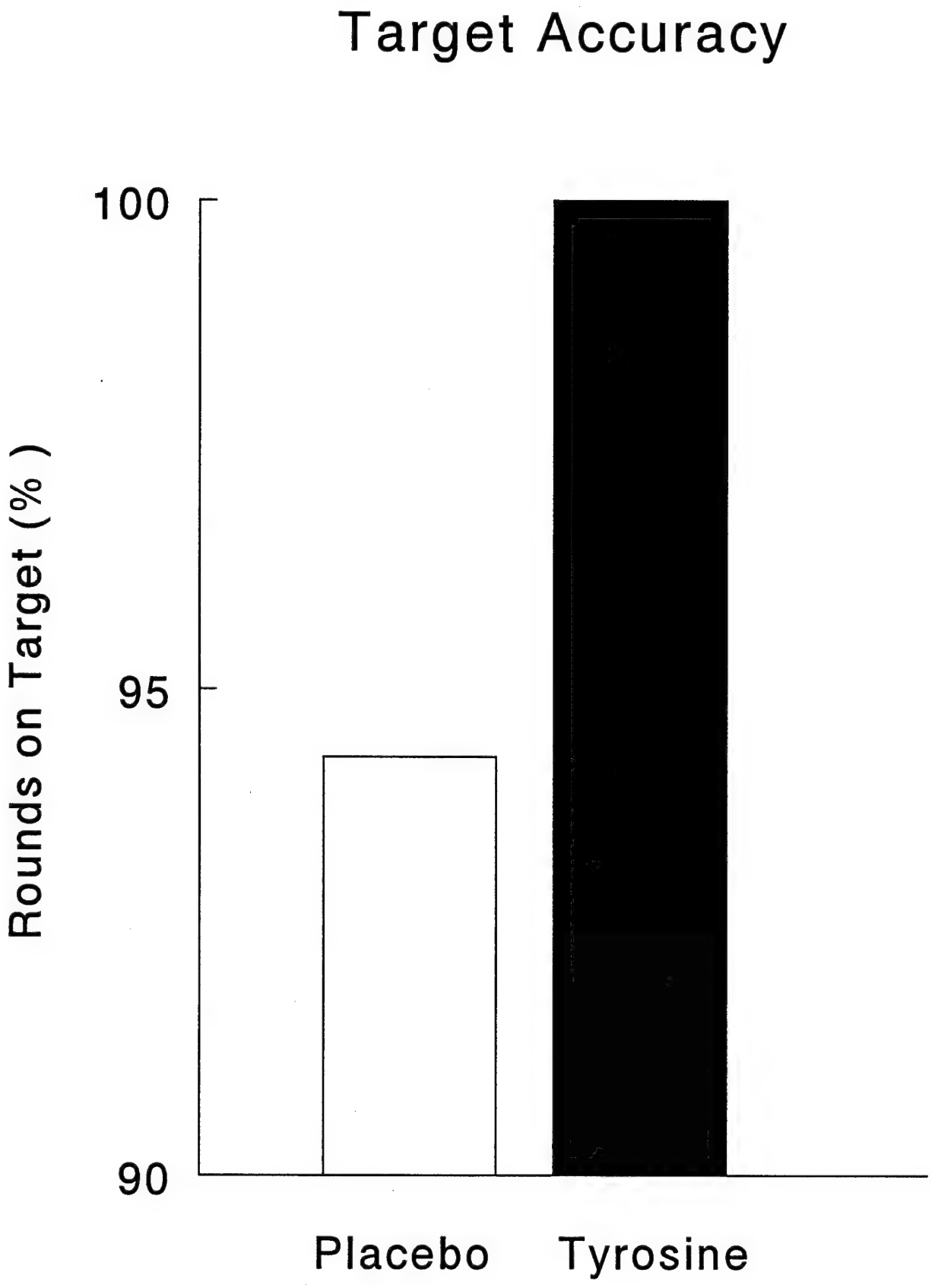

Target Accuracy
100
95
90
Rounds on Target (%)
Placebo
Tyrosine

FIGURE 5

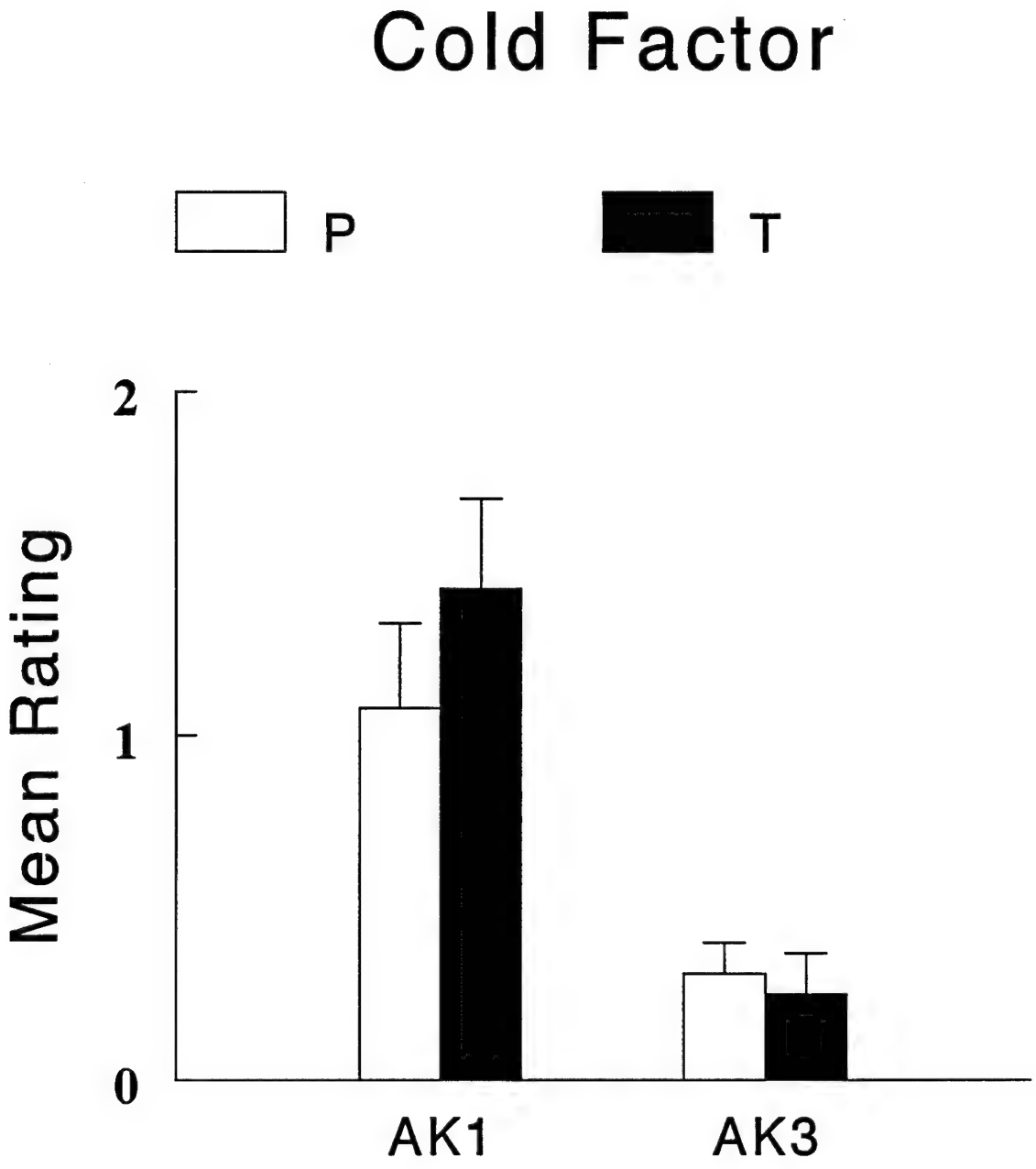
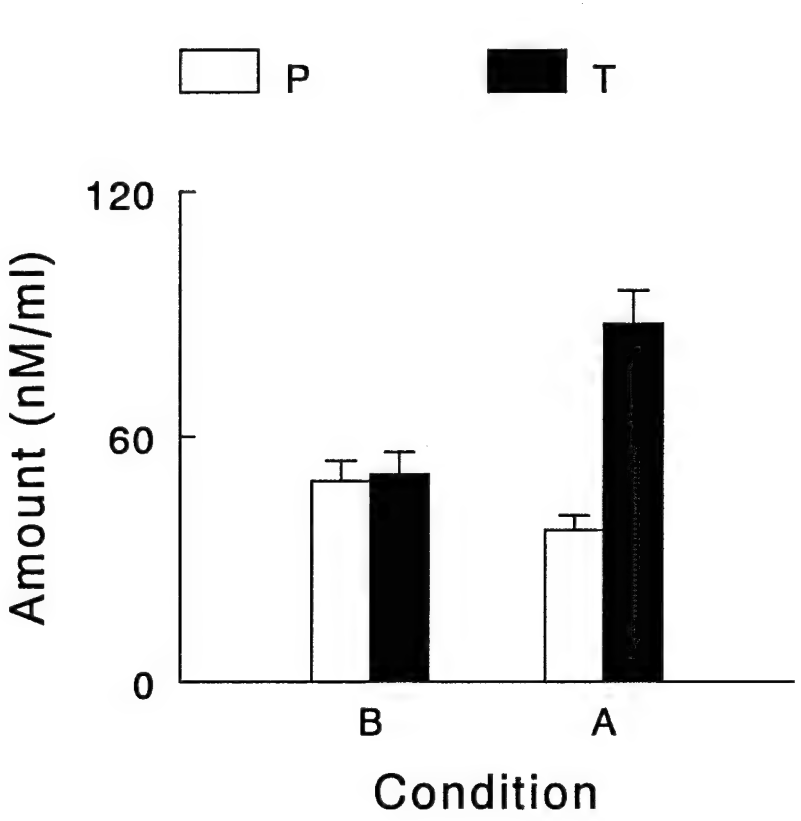
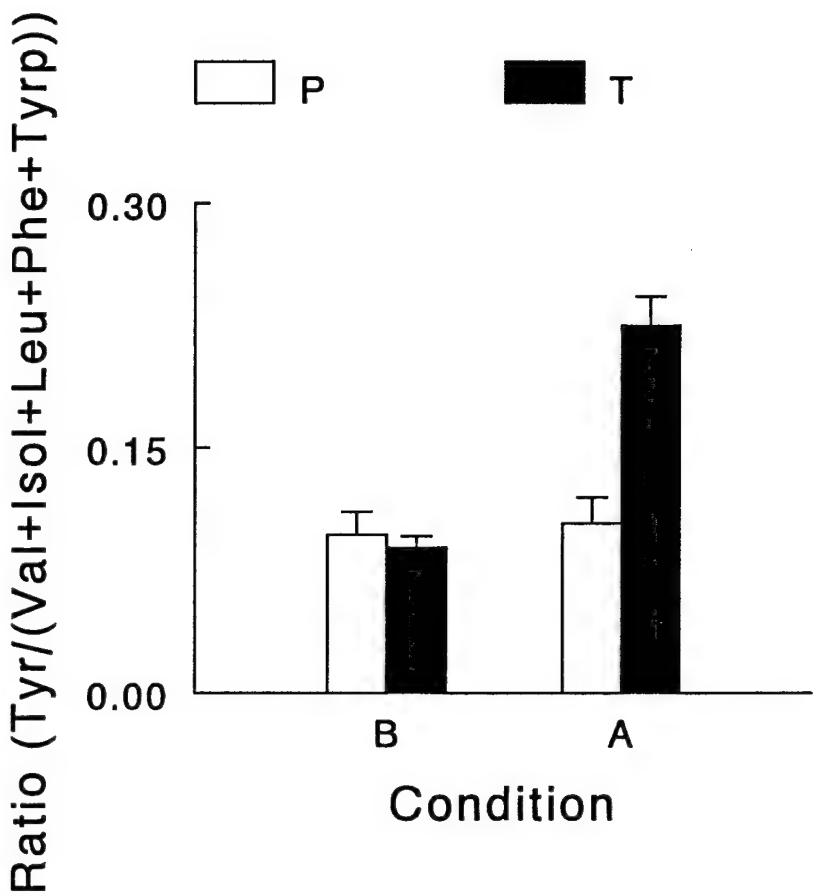


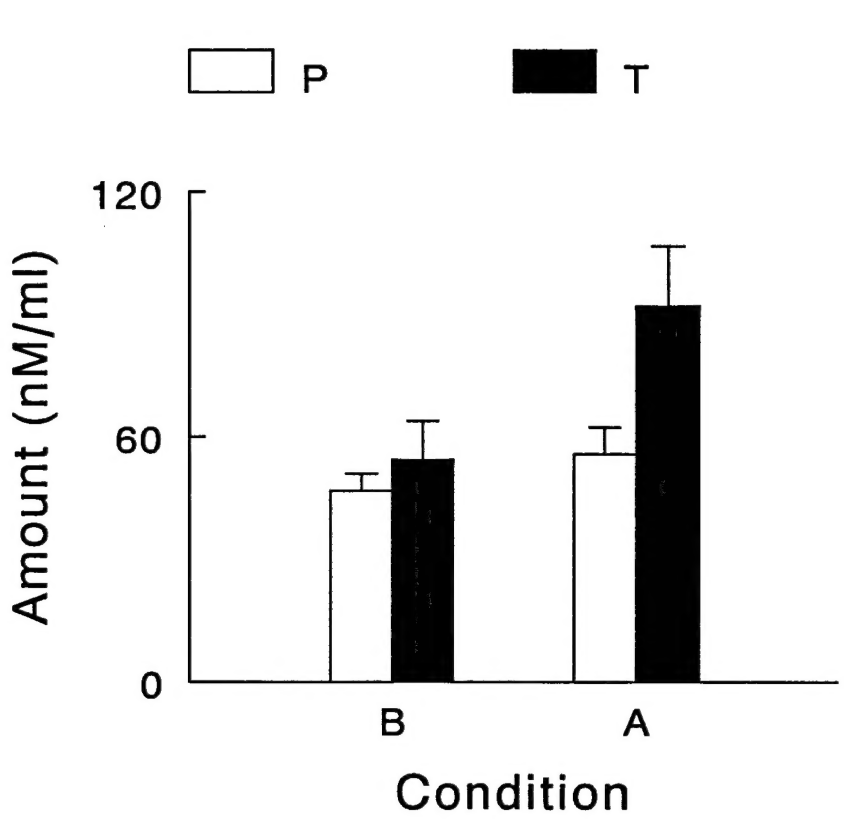
FIGURE 6

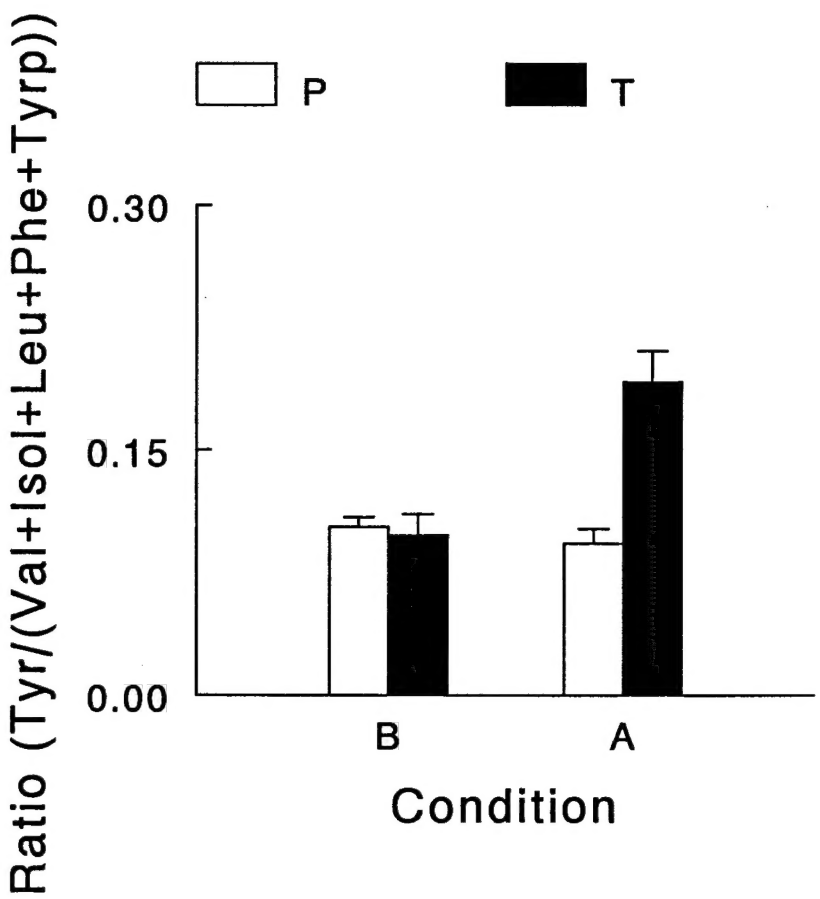
AK 1


P
T
120
60
0
Amount (nM/ml)
B
A
Condition

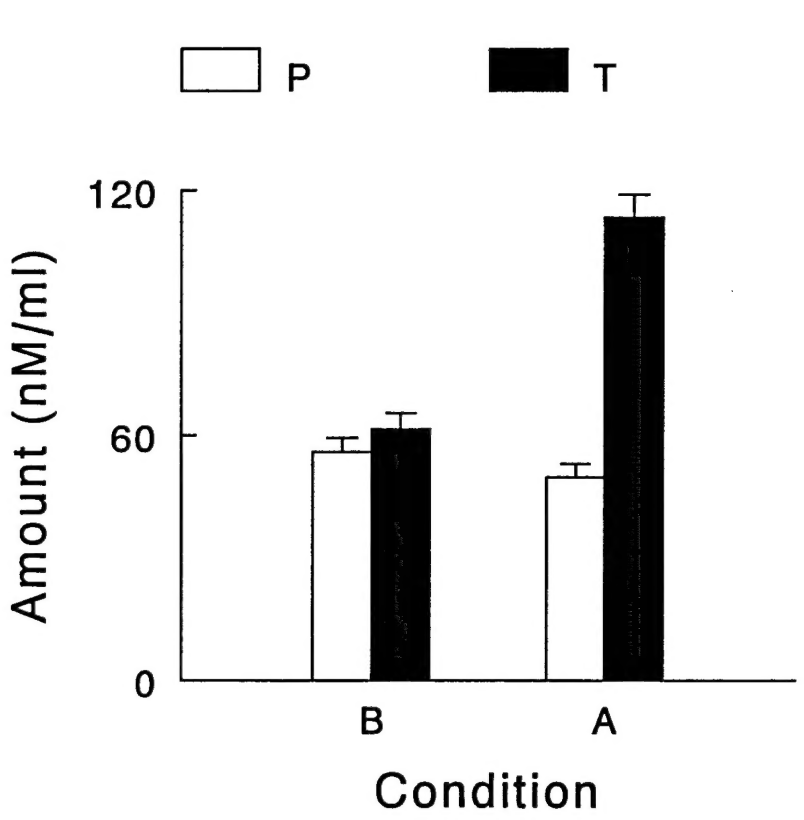

P
T
0.30
0.15
0.00
Ratio (Tyr/(Val+Isol+Leu+Phe+Tyrp))
B
A
Condition

AK 2


P
T
120
60
0
Amount (nM/ml)
B
A
Condition


P
T
0.30
0.15
0.00
Ratio (Tyr/(Val+Isol+Leu+Phe+Tyrp))
B
A
Condition

AK 3


P
T
120
60
0
Amount (nM/ml)
B
A
Condition

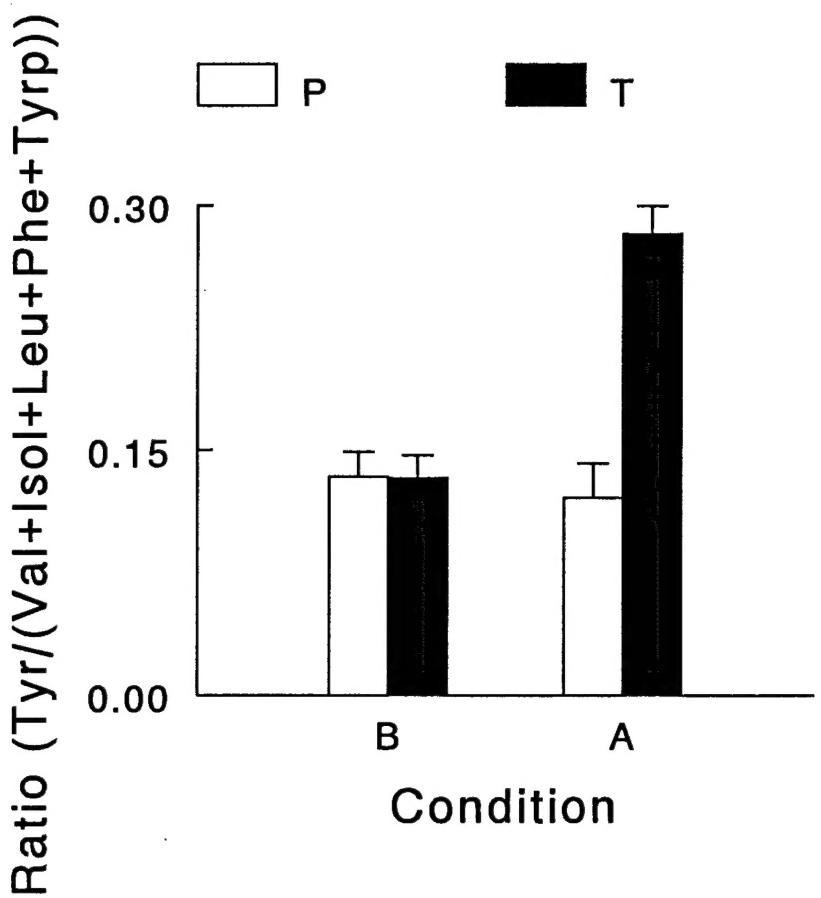

P
T
0.30
0.15
0.00
Ratio (Tyr/(Val+Isol+Leu+Phe+Tyrp))
B
A
Condition

FIGURE LEGENDS

1. Mean error responses (± SEM) committed during the repeated acquisition task. The left data column represents baseline error responding obtained at Naval Amphibious Base, Little Creek, VA (LC). The middle column represents data collected during the early stage of deployment to Alaska (AK1), and the right column represents data collected during the late stage of deployment to Alaska (AK3). The open histogram in each column represents baseline data in each location, the stripped histogram represents data from the placebo group, and the solid histogram represents data from the tyrosine group.

2. Mean response latency in seconds (± SEM) during the repeated acquisition task. The left data column represents baseline error responding obtained at Naval Amphibious Base, Little Creek, VA (LC). The middle column represents data collected during the early stage of deployment to Alaska (AK1), and the right column represents data collected during the late stages of deployment to Alaska (AK3). The open histogram in each column represents baseline data in each location, the stripped histogram represents data from the placebo group, and the solid histogram represents data from the tyrosine group.

3. Mean accuracy of responding expressed as percent correct (± SEM) during the delayed matching-to-sample task. The top panel of the figure presents data collected following the administration of placebo and the bottom panel of the figure presents data collected following the administration of tyrosine. The three groups of three histograms each represent data from the 2-, 8-, and 16-sec delay conditions, presented from left to right, respectively. Within each group of three, the histograms represent data collected during baseline (BL), the early stage of deployment to Alaska (AK1), and the late stage of deployment to Alaska (AK3), presented from left to right, respectively.

4. Target accuracy expressed as percent of rounds on target. The data were collected during the middle stage of deployment (AK2) to Alaska. The left histogram presents data collected following the administration of placebo and the right histogram presents data collected following the administration of tyrosine. These data were obtained only during the third year of the study.

5. Mean rating of perceived coldness (± SEM), on a scale of one to five, from the Environmental Symptoms Questionnaire. The left set of two histograms represents data obtained during the early stage of deployment (AK1) to Alaska and the right set of two histograms represents data obtained during the late stage of deployment (AK3) to Alaska. The left histogram of each set represents data from the placebo group and the right histogram represents data from the tyrosine group. These data represent 16 subjects obtained during the third year of the study.

6. Mean plasma tyrosine (± SEM) expressed as amount in the left panel of the figure or ratio in the right panel of the figure. The data are from the early stage of deployment (AK1) to Alaska. Amount is expressed as nanomolar per milliliter and the ratio consists of the quantity of tyrosine relative to the combined quantities of valine, isoleucine, leucine, phenylalanine, and tryptophan.

The open histograms represent data from the placebo group and the solid histograms represent data from the tyrosine group. The left set of two histograms in each panel represent data collected before tyrosine administration and the right set represents data collected 90 minutes following tyrosine administration.

7. Mean plasma tyrosine (± SEM) expressed as amount in the left panel of the figure or ratio in the right panel of the figure. The data are from the middle stage of deployment (AK2) to Alaska. Amount is expressed as nanomolar per milliliter and the ratio consists of the quantity of tyrosine relative to the combined quantities of valine, isoleucine, leucine, phenylalanine, and tryptophan. The open histograms represent data from the placebo group and the solid histograms represent data from the tyrosine group. The left set of two histograms in each panel represent data collected before tyrosine administration and the right set represents data collected 90 minutes following tyrosine administration. These data represent 16 subjects obtained during the third year of the study.

8. Mean plasma tyrosine (± SEM) expressed as amount in the left panel of the figure or ratio in the right panel of the figure. The data are from the late stage of deployment (AK3) to Alaska. Amount is expressed as nanomolar per milliliter and the ratio consists of the quantity of tyrosine relative to the combined quantities of valine, isoleucine, leucine, phenylalanine, and tryptophan. The open histograms represent data from the placebo group and the solid histograms represent data from the tyrosine group. The left set of two histograms in each panel represent data collected before tyrosine administration and the right set represents data collected 90 minutes following tyrosine administration.